EFFECT OF INJURY SEVERITY ON BRAIN ACTIVATIONS AND FUNCTIONAL CONNECTIVITY DENSITY MAPPING IN SURVIVORS OF TRAUMATIC BRAIN INJURY

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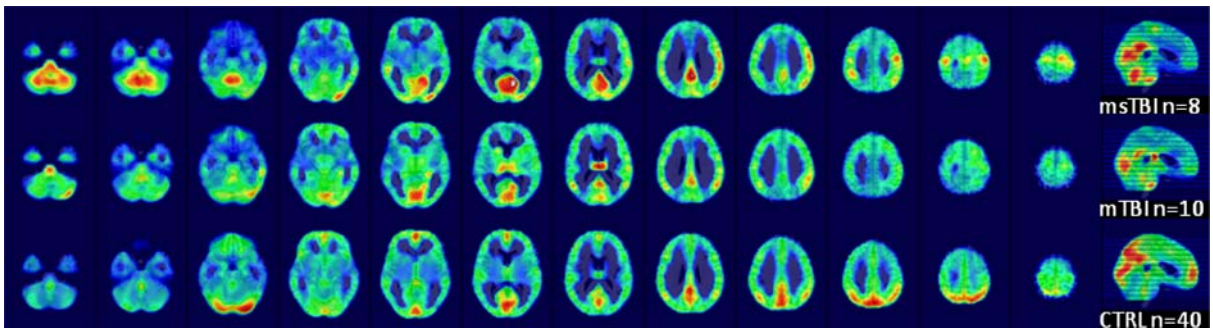
BACKGROUND: Traumatic brain injury (TBI) is a major cause of death and disability. Cognitive deficits, especially memory deficits, are extremely common in TBI survivors. These include impairment of working memory which is associated with alterations in functional cerebral activity[1]. Functional connectivity in the default mode network may also be altered due to TBI.

AIMS: To assess the influence of injury severity determined by initial Glasgow Coma Scale (GCS) on patterns of brain activation during a working memory (WM) task and resting state condition in TBI survivors compared to age and sex matched healthy controls.

METHODS: *Subjects and stimuli:* Twelve mild (mTBI), 10 moderate-severe (msTBI) TBI patients and 19 controls were scanned while performing an N-back task for letters. The task (0-, 1- and 2-back conditions) was presented using E-Prime software. Of these subjects, 10 mTBI and 8 msTBI patients were additionally scanned during a resting-state condition of 5 min in which subjects were instructed to relax and close their eyes. These patients were compared to 40 healthy control subjects from the Cambridge research site of the ''1000 Functional Connectomes'' Project (http://www.nitrc.org/projects/fcon_1000/).
MRI measurements: Brain activations were assessed with functional magnetic resonance imaging (fMRI) using a 3T MRI system (HDxt, GE) and BOLD contrast (T2* weighted gradient echo EPI sequence, TR/TE/FA 3000ms/35ms/90^{o}, 3.4x3.4x3.4 mm^3 resolution).
Processing: All functional images were realigned to the first image and normalized to the stereotactic space of the Montreal Neurological Institute (MNI) using the statistical parametric mapping package SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK). Other preprocessing steps were performed on the resting-state image time points using IDL (ITT Visual Information Solutions, Boulder, CO). These include a multilinear regression approach using the realignment parameters to minimize motion related fluctuations in the MRI signals[2], normalizing the global signal intensity across time points and band-pass temporal filtering (0.01--0.10 Hz).
The preprocessed image time series underwent functional connectivity density mapping (FCDM) to compute the strength of the local FCD (lFCD)[2]. The number of local connections at every voxel location x0, k(x0), was determined through Pearson correlations between time-varying signals at x0 and those from its closest neighbors using an arbitrary threshold $R > 0.6$[2,3].

RESULTS: Activations in the low memory load (1- vs 0-back condition, $p<0.001$ uncorrected) did not appear to be related to injury severity. High memory load (2- vs 0-back condition, $p<0.001$ uncorrected) activated Wernicke's area, inferior prefrontal gyrus, premotor cortex and dorsolateral prefrontal cortex in all groups. The TBI groups exhibited additional activations in the insular gyrus. mTBI patients further activated the middle temporal gyrus whereas the msTBI patients further activated the somatosensory association cortex and the anterior prefrontal cortex. The response to the increasing memory load (2- vs 1-back condition, $p<0.001$ uncorrected) was dependent on injury severity, whereby msTBI (but not mTBI) patients showed increased activations in the insular and middle temporal gyrus compared to controls.
In addition, TBI patients presented a different pattern of lFCD compared to healthy controls in the resting-state condition. TBI patients exhibited higher short range FCD in the cerebellum and lower short range FCD in frontal and parietal areas compared to healthy controls. Moreover, the severity of the head injury modulated the lFCD changes. Both severity injuries accounted for the reduction of the lFCD in frontal and parietal regions and for the increase of the lFCD in the thalamus, whereas only the moderate-severe injury accounted for the increase in the lFCD in the cerebellum.

CONCLUSIONS: These results indicate that TBI affects the pattern of brain activation in response to a WM task as well as the pattern of lFCD in resting-state condition; and the effects are modulated by injury severity.



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